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REVIEW

Genetics of leprosy: today and beyond

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Abstract
Leprosy is a chronic infectious disease of the skin and peripheral nerves that presents a strong link with the host genetic background. Different approaches in genetic studies have been applied to leprosy and today leprosy is among the infectious diseases with the greatest number of genetic risk variants identified. Several leprosy genes have been implicated in host immune response to pathogens and point to specific pathways that are relevant for host defense to infection. In addition, host genetic factors are also involved in the heterogeneity of leprosy clinical manifestations and in excessive inflammatory responses that occur in some leprosy patients. Finally, genetic studies in leprosy have provided strong evidence of pleiotropic effects between leprosy and other complex diseases, such as immune-mediated or neurodegenerative diseases. These findings not only impact on the field of leprosy and infectious diseases but also make leprosy a good model for the study of complex immune-mediated diseases. Here, we summarize recent genetic findings in leprosy susceptibility and discuss the overlap of the genetic control in leprosy with Parkinson's disease and inflammatory bowel disease. Moreover, some limitations, challenges, and potential new avenues for future genetics studies of leprosy are also discussed in this review.

Introduction

Leprosy caused by *Mycobacterium leprae* is one of the oldest human infectious diseases (Schuenemann et al. 2018). Despite that, the mechanisms of disease transmission remain unclear. Zoonotic transmission of leprosy has been described for armadillos while red squirrels on Brownsea Island in the UK are infected with *M. leprae* without transmission to human hosts (Truman et al. 2011; Avanzi et al. 2016; da Silva et al. 2018). Moreover, ticks and reduviid bugs have been shown to carry viable *M. leprae* and are potential disease vectors (Ferreira et al. 2018; Neumann Ada et al. 2016). Nevertheless, although zoonotic transmission can occur, the sustained prevalence of leprosy is likely a result of human to human transmission. Sole exposure to *M. leprae* is not enough to cause leprosy. The disease attack rate is low, with only a small proportion of exposed persons eventually developing leprosy (Alemu Belachew and Naafs 2019). Indeed, it is likely that a combination of environmental factors, pathogen burden, and the presence of human genetic susceptibility factors is required to lead to clinical leprosy as an outcome of exposure to *M. leprae*. Thousands of years of host–pathogen interaction in leprosy resulted in *M. leprae* losing part of its genome while maintaining proficiency in infecting and surviving within human macrophages and Schwann cells. The *M. leprae* gene decay led to strain uniformity, suggesting that the host genetic background and not bacterial variability is a central aspect of leprosy susceptibility (Cole et al. 2001). The strong link between leprosy and the host genetic background is shown by the success in identifying an array of genetic leprosy risk factors. Linkage analyses followed by positional cloning and candidate gene approaches identified multiple genes associated with leprosy (Fig. 1). However, it was the advance in molecular techniques allowing genome-wide scans in thousands of subjects that boosted the number of genes and variants identified as leprosy risk factors (Fig. 1). In this review, we describe recent genetic

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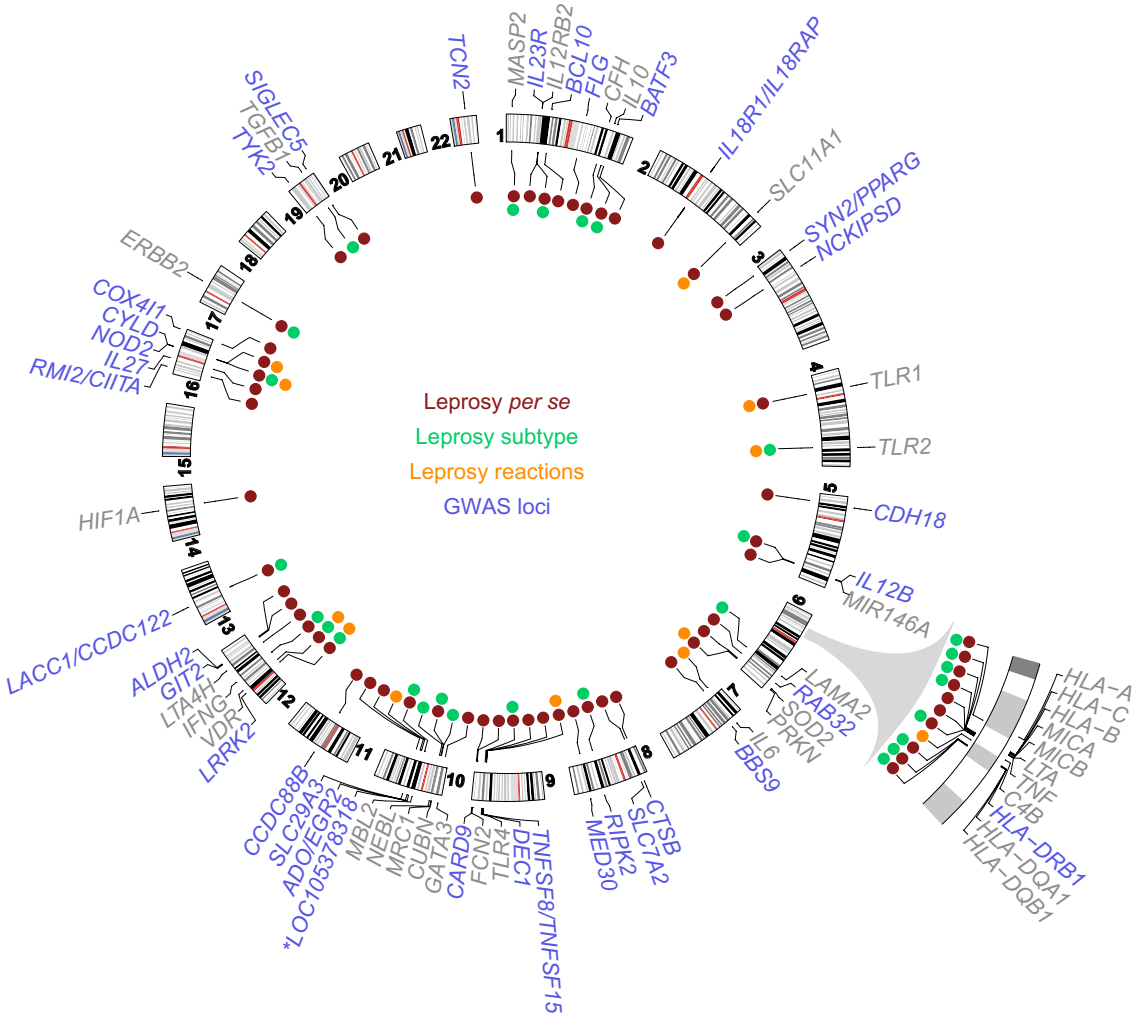

Fig. 1 Genes and GWAS loci associated with leprosy per se and leprosy endophenotypes. The human chromosomes 1–22 are presented in the circular plot. The best candidate gene in each GWAS locus is highlighted in blue, while genes identified by either candidate, positional cloning or exome approaches are given in gray. The leprosy phenotype associated in each region is denoted by colored circles linked to their corresponding loci

discoveries in the leprosy field and discuss our views for the next steps in the post-GWAS era.

Host genetics in different stages of leprosy pathogenesis

Leprosy per se

The host genetic background mediates different stages of leprosy pathogenesis ranging from innate resistance to *M. leprae* infection to control of the type and extent of host immune responses to infection. The presence of PGL-1 antibodies in serum identifies individuals exposed to *M. leprae*. However, there is no biological assay to detect patients who are pre-clinically infected with *M. leprae*. Therefore, studies assessing innate resistance to infection in leprosy are difficult to design and interpret since they rely on indirect surrogates of resistance, albeit, infection resistance may be under strong genetic control (Fava and Schurr 2016). The primary phenotype evaluated by genetic studies is broadly termed leprosy per se and refers to clinical leprosy independent of the disease subtype. Genomic variants in the promoter region of the *PRKN* (formerly *PARK2*), *IL10* and *LTA* genes and coding variants in the *TLR1, SLC11A1* (formerly *NRAMP1*) and *VDR* genes are examples of validated associations with leprosy per se (Fig. 1) (Alter et al. 2013; Alvarado-Arnez et al. 2015; Alcais et al. 2007; Marques de et al. 2013; Wong et al. 2010a; Abel et al. 1998; Fitness et al. 2004). Mechanistically, these genes have been implicated in the host immune response to pathogens. For instance, down-regulation of Parkin—encoded by *PRKN*—in macrophages

was shown to decrease the IL6 and CCL2 response to mycobacteria in a vitamin D dependent manner (de Leseleuc et al. 2013). In *M. leprae*-stimulated whole blood cultures, the absence of *PRKN* leprosy susceptibility alleles was significantly correlated with increased *IL6* and *CCL2* transcript levels (de Leseleuc et al. 2013). Moreover, increased levels of vitamin D were shown to reduce *M. leprae* viability in macrophages (Kim et al. 2018).

The first genome-wide association study (GWAS) in leprosy was published a decade ago (Zhang et al. 2009a). Multiple expansions of the GWAS population and independent replication studies helped to characterize the genetic architecture of leprosy pathophysiology (Fig. 1) (Wang et al. 2016; Liu et al. 2012, 2013, 2015a; Zhang et al. 2011). By far the most significant genetic association with leprosy per se has been located to the major histocompatibility complex (MHC). However, the identification of the molecular cause of susceptibility has been challenging due to the complex combination of amino acid variants in HLA alleles, and the strong long-range linkage disequilibrium (LD) among HLA alleles. We discuss approaches aimed to narrow the location of leprosy per se variants in HLA genes in a subsequent section. In addition, 33 non-MHC risk loci have been associated with leprosy per se by GWAS (Fig. 1) (Wang et al. 2018a; Liu et al. 2017). Among the latter, variants in the *NOD2* and *LACC1* genes were the most significantly associated risk markers, and have been replicated for the association with leprosy in independent populations (Wong et al. 2010b; Grant et al. 2012; Sales-Marques et al. 2014; Wang et al. 2018b). LACC1 directly interacts with NOD2 signaling induced by MDP, a synthetic immunoreactive peptide that mimics bacterial cell walls (Lahiri et al. 2017). The LACC1-NOD2 complex mediates mitochondrial and cellular ROS production, the secretion of proinflammatory cytokines and the cellular response to *Salmonella*, *Staphylococcus,* and BCG (Lahiri et al. 2017; Cader et al. 2016). The LACC1 amino acid change p.I254V is a strong leprosy risk factor that was shown to reduce LACC1-NOD2 signaling providing a direct link between a leprosy-risk GWAS SNP and response to infection (Lahiri et al. 2017).

The majority of leprosy per se GWAS loci was tagged by non-coding variants. Compared to amino acid changes that generally alter protein activities, non-coding variants are more likely to impact gene expression levels by disrupting transcription binding motifs or altering chromatin interactions. For instance, leprosy per se GWAS SNPs were identified as eQTLs for the *NOD2* and *IL18RAP* genes in neutrophils (Andiappan et al. 2015). More recent efforts towards the discovery of leprosy susceptibility factors focused on protein-coding variants which led to the identification of additional genes associated with leprosy (Fig. 1) (Wang et al. 2018a; Liu et al. 2017; Wang et al. 2018a). Of considerable interest was the identification of the *TYK2* p.R703W mutation as a leprosy risk factor (Liu et al. 2017). Mutations in *TYK2* such as the p.P1104A amino acid change predispose to severe and early-onset forms of tuberculosis (TB) and protect from lupus and multiple sclerosis (Boisson-Dupuis et al. 2018; Kerner et al. 2019; Cunninghame Graham et al. 2011). The association of protein-altering variants in *TYK2* with risk for both leprosy and TB and protection from autoimmune diseases suggests that this gene is a broad mediator of susceptibility to mycobacteria due to its promotional effect on the inflammatory host immune response. Hence, efficient signal transduction via TYK2 is likely an essential mechanism of host defense in leprosy. The *TYK2* p.P1104A mutation selectively disrupted IL23-dependent antimycobacterial IFNγ immunity (Boisson-Dupuis et al. 2018), and several genes that are part of the TYK2 cascade had previously been associated with leprosy. For example, a low-frequency missense variant, p.G149R of *IL23R,* and common variants near the *IL23R* gene were leprosy risk factors (Zhang et al. 2011; Liu et al. 2017; Cobat et al. 2014). Similarly, IL17, a cytokine produced via TYK2 signaling, suppressed IFN-γ induced antimicrobial activity of monocytes in response to *M. leprae* (Teles et al. 2015), and the common IL17 missense variant p.L119P was associated with leprosy susceptibility (Liu et al. 2017). In agreement with the view of TYK2 as a regulator of anti-*M. leprae* host responses, *Tyk2* knock out mice showed impaired IL12 and IL18 signalling (Shimoda et al. 2002) which is consistent with the observation that variants near the IL18 heterodimer receptors genes, *IL18R1* and *IL18RAP,* and the *IL12B* and *IL12RB2* genes are leprosy per se risk factors (Liu et al. 2012; Shimoda et al. 2002).

The studies of low frequency and rare nonsynonymous variants in leprosy per se resulted in the identification of new risk factors with high disease penetrance that had been missed by common variant GWAS. However, a caveat of the protein-coding GWAS based on exome genotyping arrays is that novel rare variants with potentially high deleterious effects can be missed due to their absence on the array. So far, only one study used whole-exome screening with next-generation sequencing (NGS) in a small subset of the samples and identified the rare p.D349N variant in the *HIF1A* gene as leprosy per se risk factor which was subsequently replicated in an independent population sample (Wang et al. 2018b). Given the cost reduction of NGS technologies, it seems reasonable to predict that we are getting to a point where the entire genome can be screened cost-efficiently for rare coding and structural variants in hundreds of samples. This will allow switching the focus from isolated rare variants to study the gene burden of rare variants to identify novel risk genes. While the study of the repertoire of rare variants will provide a higher resolution understanding of leprosy pathogenesis, added progress will also be achieved by focusing the genetic approach on extreme cases of disease

manifestation (early-onset, polarization, or reactions) where the genetic component likely has strong effects.

Leprosy polarization

Leprosy presents a spectrum of disease manifestations with clinical symptoms ranging from few well-delimited lesions with undetectable bacilli and strong host cell-mediated immune responses (tuberculoid, TT) to multiple lesions with high bacillary load and strong host humoral immune responses (lepromatous, LL). The majority of the leprosy cases are classified in three subcategories between the leprosy poles denoted as borderline leprosy (BT, BB, and BL). To standardize clinical treatment, leprosy patients are grouped into paucibacillary (PB) and multibacillary (MB) leprosy based on the number of skin lesions and peripheral nerve involvement. As *M. leprae* variability is low, the polarization of the host immune response is thought to be strongly dependent on host genetic factors. However, compared to leprosy per se the identification of genetic factors controlling immune polarization in leprosy has advanced at a slower pace. Several association studies compared leprosy subtypes against healthy controls and evaluated subtype specific effects by heterogeneity testing. Due to the low power of heterogeneity tests and the necessity to correct for the number of tests, this strategy is less powerful to detect genetic risk factors compared to contrasting subtypes (e.g. PB vs. MB) or analyzing the leprosy spectrum as a quantitative variable (TT → Borderline → LL) (Gaschignard et al. 2016). Poor phenotype definition of leprosy subtypes may also impact on findings of association studies of leprosy polarization. Some leprosy classification protocols, such as Ridley and Jopling classification, developed in 1966, require laboratory exams that are not always available in the field or are difficult to apply nowadays (Ridley and Jopling 1966). Moreover, leprosy subtype assigned to a patient may differ depending on the leprosy classification protocol applied and the physician's definition (Gaschignard et al. 2016). Hence, both misclassification of leprosy subtypes and differences in the classification method used among studies can impact on the results of association studies of leprosy polarization and replication in different populations.

Until now, most genes associated with leprosy subtypes have been identified by candidate-gene approaches and variants near *IL10*, *MBL2*, *MRC1*, *TGFB1*, *TLR2,* and *TNF* have been found to contribute to leprosy polarization (Bochud et al. 2008; de Messias-Reason et al. 2007; Santos et al. 2002; Camargo et al. 2018; Alter et al. 2010). In the first leprosy GWAS, the main 16 SNPs associated with leprosy per se were tested for association with disease polarization (Zhang et al. 2009a). The association was statistically heterogeneous between MB and PB cases for five SNPs in *RIPK2*, *LRRK2*, *LACC1/CCDC122,* and *NOD2*, where the signals were more pronounced in MB cases. In the Vietnamese population, the *LACC1* p.I254V variant identified by the GWAS was specifically associated with the MB subgroup suggesting that *LACC1* may contribute to multiple stages of leprosy pathogenesis (Grant et al. 2012). In a gene-centered fine mapping of a linkage peak on chromosome 10, SNPs near the *CUBN* and *NEBL* genes were associated with leprosy subtype in two Vietnamese population samples (Grant et al. 2014). Association studies of rare variants or GWAS specifically designed to detect genetic factors contributing to leprosy polarization could provide new insights into the human genetic architecture of host response to pathogens and serve as human model to differentiate factors directing the humoral and cell-mediated adaptive immune responses.

Excessive inflammatory responses in leprosy

One of the current priorities in leprosy control is the prevention of permanent disabilities. During the course of leprosy and even after microbiological clearance with WHO-recommended drug therapy, 30%–50% of borderline leprosy cases undergo abrupt shifts towards a pro-inflammatory response. These episodic events termed type-1 reactions (T1R) are leading contributors to host immune-mediated tissue damage and, consequently, disability in leprosy. Lepromatous leprosy cases may undergo a similar pathological immune process as T1R. However, the resulting clinical symptoms are distinct and define a separate category of leprosy reactions termed erythema nodosum leprosum (ENL). The trigger(s) of T1R and ENL are not known but are likely to involve both *M. leprae* antigens and host genetic factors. Due to its lower incidence, genetic studies in ENL are fewer compared to T1R. However, in contrast to T1R which occur within up-to 3 years of leprosy diagnosis, ENL may occur at any time after the cure of leprosy requiring a chronic care approach to leprosy management. Candidate gene approaches using small sample sizes identified alleles of the complement *C4B* gene and SNPs that regulate IL6 circulating levels associated with ENL suggesting a strong genetic component in ENL (Fig. 1) (de Messias et al. 1993). Nevertheless, assembling enough ENL samples for genome-wide approaches will require a multi-centric community effort.

The genetic factors underlining leprosy polarization or leprosy reactions can be detected by assessing subgroup heterogeneous effects (e.g. endophenotypes) (Han et al. 2016; Gaschignard et al. 2015). For instance, by contrasting T1R-affected versus T1R-free leprosy patients, the genetic associations reflected susceptibility factors for immune dysregulation that are distinct from those of leprosy per se. Although only few studies have focused on T1R, the results of these genetic studies provided a snapshot of tantalizing genetic interactions inherent to this critical inflammatory phenotype. Specifically, for

the *LRRK2* gene. the functional low-frequency p.R1628P and the common *LRRK2* p.M2357T amino acid changes were associated with T1R (Fava et al. 2016, 2019). The presence of the *LRRK2* haplotype containing the T1R-risk alleles p.1628R and p.2357M was a strong T1R-risk factor (Fava et al. 2019). The p.1628R allele was characterized by lower LRRK2 activity while p.2357M imparted a lower half-lifetime of the LRRK2 protein. Unexpectedly, a group of eQTLs counterbalanced the lower LRRK2 activity and stability of the T1R-risk haplotype by increasing *LRRK2* gene expression. However, *M. leprae* antigens abrogated the eQTL effect and reestablished the diminished LRRK2 activity of the T1R-risk haplotype (Fava et al. 2016; Manry et al. 2017).

A GWAS implementing a subgroup heterogeneity approach in search for T1R-specific effects identified eQTLs for the lncRNA *LOC105378318* associated with T1R in Vietnamese and Brazilians (Fava et al. 2017a). A suggestive association signal was also observed for SNPs near the *PPARG* gene (Fava et al. 2017a). In a candidate gene approach, two independent SNP bins encompassing the *TNFSF8* and *TNFSF15* were associated with T1R in Vietnamese and Brazilians (Fava et al. 2017b; Fava et al. 2015). Variants near the *NOD2*, *LRRK2*, *TLR1,* and *TLR2* genes were also associated with T1R (Fig. 1)(Bochud et al. 2008; Fava et al. 2016; Misch et al. 2008; Berrington et al. 2010; Sales-Marques et al. 2017). Apart from the lncRNA, all other T1R-risk genes had previously been associated with leprosy per se. Since intrinsically the biological mechanisms controlling susceptibility to leprosy per se and T1R involve genes modulating host inflammatory responses, it is possible that the same genes contribute independently to different stages of leprosy pathogenesis. For instance, when using NGS screening for rare variants in T1R-risk genes a study identified enrichment of nonsynonymous variants in the *PRKN* gene as a T1R-risk factor (Fava et al. 2019). This *PRKN* association was specific for T1R and independent of the *PRKN* promoter polymorphisms associated with leprosy per se (Fava et al. 2019). While a gene can contribute to different stages of leprosy, subgroup heterogeneity can also be a confounder. For example, T1R affects mostly MB leprosy cases. Therefore, when evaluating leprosy polarization by contrasting PB vs MB or stratifying PB and MB for sub-group comparisons with healthy controls. the association results can be misleading if there is an imbalance in the proportion of T1R cases in the two subgroups. The same is valid for leprosy per se where both leprosy subtype and leprosy reactions can be confounders leading to erroneously assigning a genetic effect to the general leprosy per se phenotype that is due to only a subgroup effect (Fava et al. 2017b; Fava et al. 2015).

The complexity of the HLA locus in leprosy susceptibility

A remarkable finding of the leprosy GWAS was the significance of association signal between leprosy per se and SNPs near Human Leucocyte Antigen (HLA) genes in the MHC region found both in Chinese and Indian populations (Wong et al. 2010a; Zhang et al. 2009a; Wang et al. 2016; Liu et al. 2015a; Liu et al. 2017). The MHC GWAS hit was several logs more significant than leprosy-associated SNPs in non-MHC regions. Interestingly, the same pattern has also been observed in GWAS of several viral and bacterial infectious diseases (International HIVCS et al. 2010; Haapasalo et al. 2018; Tian et al. 2017), highlighting the importance of the MHC region in the host response to infection (Matzaraki et al. 2017). Indeed, compared to other regions of the genome the MHC has been associated with a substantially greater number of complex and quantitative traits. HLA genes are involved not only in infectious diseases, but also in immune-mediated and neurodegenerative diseases (Matzaraki et al. 2017; Sulzer et al. 2017). Due to the role of HLA genes in T cell responses and adaptive immunity, association studies of HLA alleles with leprosy have been conducted since the 70s, mostly focused on leprosy immune polarization (Jarduli et al. 2013). Since then, the level of resolution of HLA allele typing—complicated by the extreme polymorphic nature of the genes—has improved considerably. Therefore, from the early antibody and T-cell based HLA antigen studies in leprosy to modern molecular typing approaches, there is wide variability in HLA allelic resolution (Jarduli et al. 2013). Class II *HLA-DRB1* is the classical HLA gene most tested for association with leprosy per se and leprosy subtypes (Blackwell et al. 2009). *HLA-DRB1* alleles such as *HLA-DRB1*10* and **15* have been found as risk factors, while *HLA-DRB1*04* and **09* were associated with protection from leprosy or leprosy subtypes (Jarduli et al. 2013; Hsieh et al. 2010; Zhang et al. 2009b; Vanderborght et al. 2007; Zerva et al. 1996; Tosh et al. 2006). However, in addition to *HLA-DRB1*, alleles in *HLA-A, HLA-B, HLA-C, HLA-DQB1,* and *HLA-DQA1* have also been implicated with leprosy (Fig. 1).

The combined results of studies of HLA alleles and leprosy support the involvement of classical HLA genes, especially *HLA-DRB1*, in leprosy pathogenesis. However, the causative molecular variants remain elusive, and results need to be interpreted with caution due to the existence of long-range haplotypes and possible epistasis of HLA alleles. Specifically, a high degree of polymorphic variants coupled with complex LD pattern and haplotype structures are substantial challenges in the region. Often association results of alleles in different HLA genes were

statistically equivalent due to high LD, making it very difficult to distinguish which gene was triggering the association. Indeed, differences in allele frequency and LD pattern of the HLA genes among populations might explain the lack of validation for several leprosy-associated HLA alleles. To disentangle dependent and independent signals, analysis of the genetic structure of the HLA loci in the studied population and conditional association analyses—even among class I and class II genes—are necessary for correct result interpretation. To overcome this challenge, dense fine-mapping with NGS-based high-resolution molecular HLA typing has been shown to successfully dissect genotype–phenotype correlations in complex human traits (Hirata et al. 2019). In leprosy, detailed analysis of the sample of Chinese leprosy patients employed for GWAS provided important insights into the role of HLA alleles. The GWAS genotypes were used to impute four-digit HLA alleles and association analysis with imputed HLA alleles pinpointed *HLA-DRB1*15:01* as major source of the HLA association signal for leprosy per se (Wang et al. 2016; Liu et al. 2015a). This result was consistent with several earlier candidate gene studies that had implicated *HLA-DRB1*15* as leprosy susceptibility factor. Moreover, *HLA-DRB1*15:01* was significantly more frequent in medieval skeletons of lepromatous leprosy cases when compared to contemporary and medieval controls (Krause-Kyora et al. 2018).

Even though less significant, additional independent association signals were observed for other HLA alleles after removing the *HLA-DRB1*15:01* effect (Wang et al. 2016; Liu et al. 2015a). Imputed *HLA-C*08:01* and *HLA-DQA1*03:03* were associated with leprosy per se in the Chinese population independently of *HLA-DRB1* variants (Zhang et al. 2019). Leprosy association signals in the MHC region statistically independent from *HLA-DRB1* were found in Vietnamese and Indian samples (Alcais et al. 2007; Alter et al. 2011). Two independent association signals with leprosy were located in the MHC class I region, including one SNP in high LD with the *HLA- C*15:05* allele (Alter et al. 2011). Interestingly, MHC class III genes were also associated with leprosy pathogenesis. Fine-mapping of the class III region in a Vietnamese sample detected a functional variant in the *LTA* gene associated with leprosy susceptibility (Alcais et al. 2007). The association of *LTA* was stronger in cases of early-onset leprosy and was not impacted by removing the effect of *HLA-DRB1* variants. Additional HLA genes within the MHC region were associated with leprosy phenotypes by candidate gene approaches, including *TNF* in the class III region as well as *MICA* and *MICB* in MHC class I (Fig. 1) (Tosh et al. 2006; do Sacramento et al. 2012; Cardoso et al. 2011; Areeshi et al. 2017). Taken together, these studies suggested the presence of multiple independent MHC signals associated with leprosy phenotypes, including but not limited to the antigen-presenting class I and class II HLA molecules.

Pleiotropic effects in leprosy

The selective pressures experienced by past human–pathogen interactions favored the positive selection of variants enhancing the effectiveness of adaptive and innate immune response genes in fighting pathogens (Barreiro and Quintana-Murci 2010). A tantalizing question that has emerged from recent research is to what extent is the increased incidence of immune-mediated and neurodegenerative diseases a reflection of past pathogen adaptation (Bach 2002; Savica et al. 2016). Recent studies identified a correlation between variants that were beneficial in the host response to infection with those that increase the risk of immune-mediated diseases. With the study of an ever-increasing number of human phenotypes by GWAS approaches the cumulative evidence increasingly demonstrates pleiotropic effects of genomic variants in infectious diseases, immune-mediated diseases, and neuropsychiatric disorders (Han et al. 2016; Barreiro and Quintana-Murci 2010). In this context, leprosy is a good human model to study pleiotropic effects for infection (leprosy per se), immune responses (polarization), and pathological inflammation and nerve damage (T1R and ENL). GWAS approaches have identified a remarkable overlap between genes associated with leprosy per se and inflammatory bowel disease (IBD; Fig. 2). However, there was no consistency between pleiotropy (same risk alleles) or antagonistic pleiotropy (opposite risk alleles) for the overlapping variants. For instance, non-coding variants near the *RIPK2* gene and the *LACC1* p.I254V amino acid change were risk factors for both leprosy per se and Crohn's disease (CD), a type of IBD (Liu et al. 2015a). Conversely, leprosy per se risk SNPs in the *IL12B* and near the *IL18* receptor genes cluster were protective for IBD. Antagonistic pleiotropy is expected from the evolutionary point of view, e.g. *TKY2* p.P1104A increased risk of TB and protected from multiple sclerosis and lupus (Boisson-Dupuis et al. 2018; Kerner et al. 2019; Cunninghame Graham et al. 2011), while pleiotropy is more complex to understand and suggests that the same mechanisms are involved in clinically diverse diseases. The intriguing overlap of IBD and leprosy, which encompasses both pleiotropic and antagonistic pleiotropic gene variants, might occur at different levels of disease pathogenesis. At a first stage, variants could module susceptibility to microorganisms (IBD = leprosy per se). For instance, selected IBD-risk variants could unbalance the interplay between the host immune response and gut microbiota favoring the propagation of selected species of bacteria (Imhann et al. 2018). This dysbiosis precedes the onset of IBD clinical symptoms suggesting an impaired host

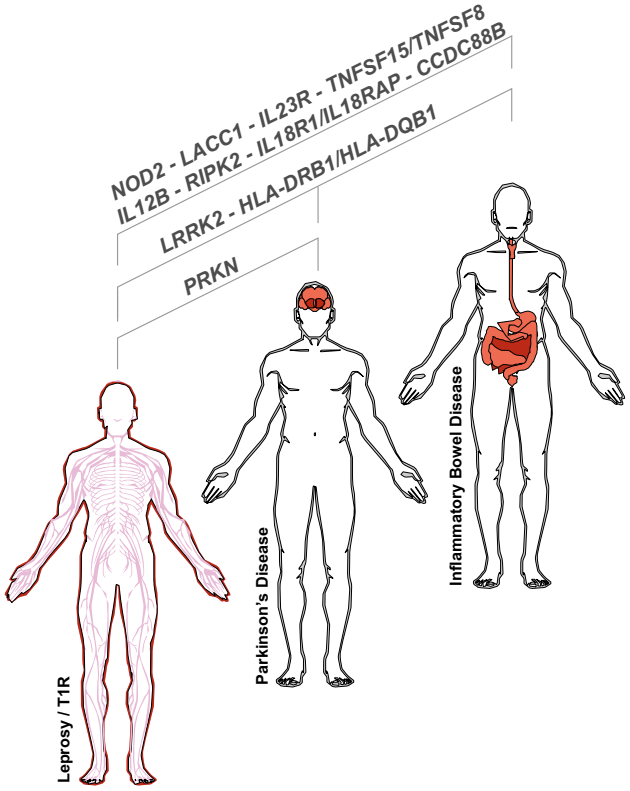

Fig. 2 Genes with pleiotropic effect in leprosy. The figure highlights the genes with pleiotropic effects in PD, IBD or leprosy/T1R. The anatograms indicate the tissue most affected in each phenotype with the skin and peripheral nerves in Leprosy/T1R, basal ganglia and substantia nigra in the brain of PD cases, and the gastrointestinal tract in IBD. A link between the anatograms underlines genes with genomic variants presenting pleiotropic effects

response leading to dissemination of even commensal bacteria (Imhann et al. 2018). Genes involved in this dysbiosis include *NOD2* and *CARD9* both associated with leprosy per se (Liu et al. 2017; Sales-Marques et al. 2014). The extent of inflammatory response to the unbalance in the proportion of gut bacterial species could be modulated by a separate set of genomic variants (IBD = T1R). An example is the *TNFSF15* and *TNFSF8* gene cluster as T1R-risk variants presenting the same risk allele observed in IBD (Fava et al. 2017b; Liu et al. 2015b).

Consistent with the two-stage hypothesis of variant selection in IBD and leprosy, when pleiotropic effects were assessed for SNPs nominally significant in the T1R GWAS, 10.6% of 232 SNPs representing the main IBD GWAS loci presented the same risk alleles as the T1R phenotype (Fava et al. 2017; Jostins et al. 2012). In the T1R-free leprosy subset, the enrichment for pleiotropic effect was less pronounced (6.2%) suggesting that although there is an overlap of IBD and leprosy per se IBD is genetically closer to excessive immune reactivity represented by T1R. The comparative GWAS analysis for T1R in Vietnamese and IBD in Caucasian patients only considered the top SNP in each IBD locus, which does not need to be the causative variant. Therefore, the genetic overlap and extent of pleiotropy, between T1R and IBD is likely underestimated since ethnicity dependent changes in linkage disequilibrium were not considered. Another interesting point was that although the lncRNA *LOC105378318* associated with T1R was not detected by IBD GWAS this lncRNA is mostly expressed in the ileum and colon, the two most commonly affected tissues in IBD (Fava et al. 2017a; Consortium GT 2015). lncRNAs can act as competing endogenous sequences (Tay et al. 2011). The lncRNA *LOC105378318* contains two 7mer-A1 sites that are seed regions for miR-346 and miR-486-5p, respectively (Das et al. 2014). Interestingly, miR-486-5p was downregulated in skin biopsy of leprosy patients while miR-346 controlled TNF release in IBD and rheumatoid arthritis, and has been suggested as a biomarker for pulmonary *M. avium* complex infection (Soares et al. 2017; Semaan et al. 2011; Chen et al. 2014; Nishimura et al. 2017). The interplay between *LOC105378318* and miR-486-5p and miR-346 is thus a possible mechanism of major control of pathological inflammation mediated by pathogens.

Another interesting finding of genome-wide scans was the association between *LRRK2* and *PRKN* variants with leprosy phenotypes. Mutations in the *LRRK2* gene are the most common cause of idiopathic PD while deleterious homozygous mutations and structural variants in *PRKN* are causal for early-onset PD (EOPD). Therefore, it is tempting to speculate that independent biological processes culminate in shared clinical symptoms of PD. In this context, studying pleiotropic effects in T1R/leprosy and PD can help to disentangle some of the key functions of the promiscuous LRRK2 and Parkin proteins.

The biological consequence of *LRRK2* mutations is tied to the protein domain where they occur. Moreover, as gene–gene interactions are cell-specific, the extent of the biological impact of LRRK2 mutations is dependent on the presence or modifications of its interactors (Beilina et al. 2014). For instance, the clearance of trans-Golgi derived vesicles by autophagy is dependent on LRRK2 complex including proteins of the PD-risk genes *GAK*, and *RAB7L1* (Beilina et al. 2014). The lack of any protein of the complex impaired LRRK2 mediated autophagy. Pathogenetic mutations in LRRK2 enhanced the autophagy impairment (Beilina et al. 2014). Consequently, LRRK2 functions are not only impacted by LRRK2 amino acid changes but also by its cellular interactors. The LRRK2 p.R1628P mutation endows a gain of kinase activity similar to the PD causal p.G2019S mutation and displays antagonistic pleiotropy for T1R and PD (Fava et al. 2019; Shu et al. 2016). Given the critical role of the cell interactome for LRRK2 function, it is possible that the same mutation in the periphery

will lead to increased ROS production and abrogation of apoptosis in response to mycobacteria while in the central nervous system it will lead to defective autophagy and lysosome acidification (Hui et al. 2018). The LRRK2 p.G2019S mutation correlated with the presence of Lewy bodies, a protein precipitate which has α-synuclein as its main component, that are a neuropathological hallmark of PD (Kalia et al. 2015). Interestingly, the leprosy per se risk allele *HLA-DRB1*15:01* recognized epitopes of α-synuclein resulting in enhanced immune reactivity (Fig. 2) (Sulzer et al. 2017).

Contrary to *LRRK2* variants, *PRKN* mutations implicated in PD were observed more than expected by chance in T1R affected subjects suggesting overlapping mechanisms of inflammation in the central and peripheral nervous systems (Fig. 2). The question raised by *PRKN* pleiotropy in T1R and PD is if infectious triggers are necessary for the manifestation of both diseases. T1R is intrinsically dependent on previous or current infection with *M. leprae* while an infectious component in PD is controversial. Of note, rifampicin used to treat mycobacterial infections including leprosy per se has been suggested as a potential drug for PD treatment (Bi et al. 2013). Parkin and PINK1 signaling is critical for clearance of damaged mitochondria and disruption of Parkin/PINK1 signaling increased mitochondrial antigen presentation to the immune system linking PD to pathological inflammation (Matheoud et al. 2016). Moreover, *pink1* knock out mice challenged with intestinal Gram-negative bacteria engaged mitochondrial antigen presentation resulting in immune-mediated neuronal destruction. Hence, these results linked a peripheral gut pathogen with neuronal damage in the brain (Matheoud et al. 2019). Parkin/PINK1 signaling is likely an important checkpoint in disease tolerance and impairment in the signaling may cause dysregulated inflammation both in the periphery (T1R) and in the central nervous systems (EOPD).

Leprosy post-GWAS era

Despite that leprosy GWAS have now being carried out with thousands of samples, part of the estimated genetic heritability in leprosy is still missing (Wang et al. 2016). Exclusive focus on the impact of common variants may explain, at least in part, the missing heritability. Studies designed to evaluate the burden of deleterious rare variants are promising; however, the statistical power and cost per sample are still a limitation of NGS approaches at the genome-wide level. One way to address both of these limitations is by extensive characterization of cases aiming to reduce phenotypic heterogeneity. Identifying subsets of samples with high likelihood of a strong genetic component, e.g. pediatric onset of leprosy or comparing extremes in leprosy polarization, might increase the chances of success of rare variant burden analyses. Moreover, by studying families with exceptionally rare presentations of the disease, distinct from typical leprosy cases, or rare instances of leprosy recurrence, one might identify genes that can be reevaluated in the general population. In addition, types of genomic variation different from SNPs are poorly explored in leprosy. Structural variants including extended deletions or duplications might contribute to leprosy susceptibility through gene dosage effects. Surpassing genetics and moving to genomics, epigenetic modifications in *M. leprae* infected host cells might also contribute to disease susceptibility. By evaluating the epigenetic landscape of Schwann cells and macrophages in response to *M. leprae* one might capture the bridge between genetic variation, genomics and the environment.

As observed in other infectious diseases (Schurz et al. 2019), leprosy is more frequent in men than women. To date, no large-scale study reported the contribution of genetic factors for the sex bias in leprosy. While social and behavioral factors might contribute to the male bias in leprosy, the role of variants on sex chromosomes has not been studied. Sex chromosomes are commonly filtered from GWAS analysis due to the complexity of analyzing dosage effects due to X inactivation by *XIST*. Yet, the X chromosome harbors several immune-related genes that might contribute to sex bias in leprosy (Jaillon et al. 2019). As extensively discussed, the genetic overlap between leprosy/T1R with IBD and PD is a venue that if explored in more detail could improve our understanding of broad mechanisms of the host response to infection and the regulatory pathways of inflammation. While leprosy can be a model for common immune-mediated diseases, it is equally important to highlight how the leprosy field can benefit from studies in much better-funded phenotypes such as PD and IBD. For instance, leprosy reactions could be managed by repurposing existent IBD drugs. While Infliximab, used to treat IBD, has been successfully used to treat ENL (Faber et al. 2006), this option is still quite costly. By comparing the shared component of leprosy reactions and IBD one could narrow down the list of IBD drug targets aiming to replace long treatment with prednisolone or thalidomide as the gold standard in leprosy reactions. Similarly, the expanding array of LRRK2 inhibitors for the management of PD might find another useful application in the field of leprosy reactions. Taken together, these examples show the benefits that may be derived for both common and rare immune-mediated diseases by deciphering their shared mechanistic pathways.

Compliance ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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